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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/428,371 | 10/28/1999 | DAVID M. SODERLUND | 19603/606-(C | 4568 |

7590 09/24/2003

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| EXAMINER |
|---|
| ZARA, JANE J |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1635 | 25 |

DATE MAILED: 09/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

F4

# Office Action Summary

| Application No. | Applicant(s) |
|---|---|
| 09/428,371 | Soderlund et al |
| **Examiner** | **Art Unit** |
| Jane Zara | 1635 |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1) ☒ Responsive to communication(s) filed on *Jun 30, 2003* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

**Disposition of Claims**

4) ☒ Claim(s) *41-52 and 78-83* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *41-52 and 78-83* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

This Office action is in response to the communications filed June 30, 2003, Paper Nos. 23 and 24.

Claims 41-52 and 78-83 are pending in the instant application.

*Request for Continued Examination*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after non-final rejection. This application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid. Applicant's submission filed on June 30, 2003 has been entered.

***Response to Arguments and Amendments***

Any rejections not repeated in this Office action are hereby withdrawn.

*New Rejections*

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 42-46 and 48- 52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 42, 43, 48 and 49, line 1, it is unclear which cell is being referred to (e.g. inserting --host-- before "cell" would be remedial.

In claims 45, 46, 51 and 52, line 1, "said evaluation" lacks proper antecedent basis (e.g. replacing "said" with --the-- would be remedial).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 41-52 and 78-83 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of screening a chemical agent for its ability to modify sodium channel function in a host cell in vitro, does not reasonably provide enablement for screening a chemical agent for its ability to modify sodium channel function in a host cell in vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to methods of screening chemical agents for their ability to modify sodium channel function, comprising introducing an isolated nucleic acid molecule encoding a voltage-sensitive sodium channel of Musca domestica, which said nucleic acid molecule hybridizes to a nucleic acid molecule having a nucleotide sequence of SEQ ID NO: 1 or 2, or encoding an

amino acid sequence of SEQ ID No: 3 or 4, at 42°C with 5 x SPCC and 50 percent formamide with washing at 65°C with 0.5 x SSPC in a host cell in vivo or in vitro.

**The state of the prior art and the predictability or unpredictability of the art.** The following references are cited herein to illustrate the state of the art of nucleic acid delivery in organisms. Branch and Crooke teach that the in vivo (whole organism) application of nucleic acids is a highly unpredictable endeavor due to target cell accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of *in vivo* delivery and expression of nucleic acids. (See entire text for Branch and especially pages 34-36 for Crooke). The high level of unpredictability regarding the prediction of efficacy nucleic acid expression in providing treatment effects was illustrated in the clinical trial results obtained by ISIS pharmaceuticals for the treatment of Crohn's disease using antisense targeting ICAM-1, whereby the placebo treatment was found more successful than antisense treatment (BioWorld Today: See entire article, especially paragraphs 3 and 5-7 on page 1). Additionally, Palu et al teach that the success of gene delivery using virally derived vectors is dependent on the empirical determination of successful gene transduction for a given vector and a given target cell (See entire article, especially page 4, section 2.)

Tamm et al, in a review article discussing the therapeutic potential of antisense in treating various forms of neoplasia, conclude that "Proof of clinical efficacy, of any of the antisense oligonucleotides in the field of oncology, is still missing." (see especially pages 490-493 for a summary of various clinical trials in process using antisense). Additionally, Agrawal et al point to

various factors contributing to the unpredictability of antisense therapy, including non-antisense effects attributed to secondary structure and charge, as well as biological effects exerted by sequence motifs existing within the antisense sequences, all providing for unpredictable in vivo side effects and limited efficacy (e.g. see pages 72-76). Agrawal et al speak to the unpredictable nature of the antisense field thus: "It is therefore appropriate to study each antisense oligonucleotide in its own context, and relevant cell line, without generalizing the results for every oligonucleotide." (see page 80). Cellular uptake of antisense oligonucleotides by appropriate target cells is another rate limiting step that has yet to be overcome in achieving predictable clinical efficacy using antisense. Both Chirila et al and Agrawal et al point to the current limitations which exist in our understanding of the cellular uptake of nucleic acids in vitro and in vivo (see Agrawal et al especially at pages 79-80; see Chirila et al in its entirety, especially pages 326-327 for a general review of the "important and inordinately difficult challenge" of the delivery of therapeutic antisense oligonucleotides to target cells).

**The amount of direction or guidance presented in the specification AND the presence or absence of working examples**. Applicants have not provided guidance in the specification toward a method of screening chemical agents for modifying sodium channel function in vivo. The specification teaches methods of screening chemical agents for their ability to modify sodium channel function, comprising introducing in vitro to an appropriate host cell an isolated nucleic acid molecule encoding a voltage-sensitive sodium channel of Musca domestica, which said nucleic acid molecule hybridizes to a nucleic acid molecule having a nucleotide

sequence of SEQ ID NO: 1 or 2, or encoding an amino acid sequence of SEQ ID No: 3 or 4, at 42°C with 5 x SPCC and 50 percent formamide with washing at 65°C with 0.5 x SSPC in a host cell The specification fails to teach such screening methods in an organism. One skilled in the art would not accept on its face the examples given in the specification of the in vitro screening methods as being correlative or representative of the successful screening of chemical agents for their ability to modify sodium channel function in an organism in view of the lack of guidance in the specification and known unpredictability associated with gene delivery and expression in an appropriate host cell in vivo and further whereby voltage-sensitive sodium channel function is modified. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with in vivo delivery and expression of recombinant nucleic acids and further whereby voltage-sensitive sodium channel function is modified in host cells in an organism.

**The breadth of the claims and the quantity of experimentation required**. The breadth of the claims is very broad. The claims are drawn to methods of screening chemical agents for their ability to modify sodium channel function, comprising introducing an isolated nucleic acid molecule encoding a voltage-sensitive sodium channel of Musca domestica, which said nucleic acid molecule hybridizes to a nucleic acid molecule having a nucleotide sequence of SEQ ID NO: 1 or 2, or encoding an amino acid sequence of SEQ ID No: 3 or 4, at 42°C with 5 x SPCC and 50 percent formamide with washing at 65°C with 0.5 x SSPC in a host cell in vivo or in vitro. The quantity of experimentation required to practice the invention as claimed would require

the *de novo* determination of accessible target sites, modes of delivery and formulations to target appropriate cells and /or tissues whereby voltage-sensitive sodium channel function is altered in an organism. Since the specification fails to provide any particular guidance for such assay methods in an organism, and since determination of the factors required such in vivo nucleic acid expression and chemical screening is highly unpredictable, it would require undue experimentation to practice the invention over the broad scope claimed.

***Conclusion***

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(703) 306-5820.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (703) 305-3413. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

*JZ*

September 22, 2003

RAM R. SHUKLA, PH.D.
PRIMARY EXAMINER